REMARKS

No amendments have been made to the Claims herein. Claims 14, 19-28, 30, and 33-44 remain pending and currently under consideration.

REJECTION UNDER 35 USC §112

Applicant appreciates the Examiner's withdrawal of the rejection under 35 USC §112, first paragraph.

INFORMATION DISCLOSURE STATEMENT

The Office Action indicated that documents #2 and #3 cited in the IDS and considered 07/23/2007 were no longer considered. Further, the Office Action indicated re-submission of the documents and any missing element(s) will be the date of submission for purposes of determining compliance with the requirements under 37 CFR 1.97(e).

It is believed that a date for documents listed as #2 and #3 in the IDS was not necessary for consideration of the documents or relevant to the document submission for prior art purposes, and the references should be considered as of the first submission. Documents #2 and #3 were submitted in support of the fact that experiments described in Yoo et al. and Kang et al. were carried out at in the same laboratory of Dr. Rudolph Juliano at the University of North Carolina, Department of Pharmacology. This information can be obtained from the Yoo et al. and Kang et al. documents themselves, and the submission of documents #2 (Rudolph L. Juliano laboratory description web page at http://www.med.unc.edu/pharm/faculty/juliano.htm) and #3 (Juliano lab members web page at http://www.med.unc.edu/pharm/rjlabpg/previous.htm) was merely reinforcement of such fact. See Amendment and Response filed May 3, 2007, at page 13; Yoo et al.; and Kang et al.

Furthermore, the initial indication of the Office Action mailed July 26, 2007 was that cited references #2 and #3 were fully considered and entered. While a formal indication of consideration may be withdrawn, once a reference is reviewed and considered, it is not believed that such consideration can be eliminated for purposes of knowledge of information previously entered and fully considered.

In an effort to address concerns relating to the formality of including a date in Form 8b, Applicant submits herewith duplicate copies of documents #2 and #3, in conjunction with a supplemental Form 8b, which includes the date of access of each of the objected references. Applicant submits the present submission is timely as it is being provided in response to Applicant's first notice of objection of missing elements. Reconsideration of the objection and reinstatement of the indication of consideration of documents #2 and #3 is respectfully requested.

REJECTIONS UNDER 35 USC §102

Rejection under 35 USC §102(b) over Szoka et al.

Claims 14, 19, 38, 39 and 43 were rejected under 35 USC §102(b) as anticipated by Szoka et al. (US Patent No. 5,661,025). The Office Action maintains Szoka et al. teach DNA, RNA and RNA:DNA hybrid molecules wherein the molecules are mixed with PAMAM dendrimers having generations 2 to 5; and absent any evidence to the contrary, the molecules taught by Szoka et al. are capable of mediating RNAi. See Office Action, at page 4, third paragraph. Applicant respectfully traverses the rejection.

First, Applicant submits the standard asserted in the Office Action in connection with the anticipation rejection is improper. The Office Action provides only a conclusory statement that the disclosure provided in Szoka et al. anticipates the present invention. In order to effectively anticipate an invention, a reference must disclose, either explicitly or inherently, each and every element of the claimed invention. See MPEP 2131. The Office Action does not provide a showing that each and every element of the claimed invention is disclosed in Szoka et al., whether explicitly or inherently.

Furthermore, in order to establish a *prima facie* case of anticipation based on an inherent characteristic, the Examiner must provide rationale or evidence tending to show inherency of a certain result or characteristic. See MPEP 2112. "The examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Additionally:

> *The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.* In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981); and
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> *Inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.* In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Applicant submits the present Office Action merely concludes DNA, RNA and RNA:DNA hybrid molecules mixed with PAMAM dendrimers having generations 2 to 5 are disclosed. No rationale to show that the molecules taught by Szoka et al. are necessarily capable of mediating RNAi is provided. Thus, the burden should not shift to Applicant to establish a difference between the molecules of Szoka et al. since no evidence tending to show that the molecules taught by Szoka et al. are capable of mediating RNAi, has been established, whether by explicit or inherent disclosure of Szoka et al.

In an effort to advance prosecution, however, Applicant offers the following additional discussion further rebutting Szoka et al. as an anticipatory disclosure. For example, Szoka et al. describes "single

stranded polynucleotides or 'therapeutic strands' include antisense polynucleotides (DNA and RNA), ribozymes and triplex-forming oligonucleotides." See column 9, lines 24-26. Applicant submits this disclosure provided in Szoka et al. evidences that the molecules taught by Szoka et al. cannot inherently anticipate the present invention, since it demonstrates that polynucleotide molecules taught by Szoka et al. have at least one or more results or characteristics which do not include mediating RNAi. At the very best, the disclosure of Szoka et al. teaches molecules that may be capable of mediating RNAi, certainly not that molecules mediating RNAi necessarily flow from the teaching of Szoka et al. Therefore, the disclosure of Szoka et al. does not provide an effective reference for inherent anticipation of the present invention.

Second, while Applicant maintains that molecules described in Szoka et al. do not necessarily mediate RNAi, even if they did necessarily mediate RNAi, Szoka et al. still does not anticipate the present invention. It turns out the experiments of Szoka et al. do not demonstrate an effective delivery mixture comprising a generation 2 to 5 dendrimer mixed with a nucleic acid to deliver an active nucleic acid to cells. Applicant submits herewith a journal publication co-authored by Jean Haensler and Francis C. Szoka, Jr. which corresponds to the disclosure and Examples 1-16 of Szoka et al. US Patent 5,661,025 (See J. Haensler and F.C. Szoka, *Bioconjugate Chem.* 4: 372-379. 1993.). Compare, Examples 1-11 of Szoka et al. to Experimental procedures descriptions at page 372, last paragraph of second column through page 374, first paragraph of second column of Haensler and Szoka; and compare Examples 12 through 16 of Szoka et al. to Results discussions at page 374, second paragraph of second column, through the first partial paragraph on page 377, respectively. Additionally, Applicant submits herewith a follow-on journal publication authored by Francis C. Szoka, Jr. and colleagues, wherein the results of Haensler and Szoka are contradicted, indicating that "on further study, we find that stringently synthesized and purified, mono-disperse PAMAM dendrimers exhibit only low levels of transfection." See M.X. Tang et al., *Bioconjugate Chem.* 7: 703-714. 1996, at page 703, second paragraph of Introduction.

Furthermore, the results of Haensler and Szoka as well as Tang et al. were discussed in a 2000 review article describing the use of dendrimers for delivery of genetic material. See J.D. Eichman, A.U. Bielinska, J.F. Kukowska-Latallo and J.R. Baker, Jr. *P.S.T.T.* 3: 232-245. 2000. The results of Haensler and Szoka were summarized, pointing out that further work (published in Tang et al.) demonstrated the initial observed results were mediated by degraded dendrimers; and the exact structures accounting for observed results and efficacy conferring enhanced transfection activity are still unknown. See Eichman et al. at page 237, last paragraph through page 238, first paragraph.

Eichman et al. also describes results in contrast to those described in Haensler and Szoka, wherein intact dendrimers have been documented as conferring effective delivery of genetic material into

cells. See Eichman et al. at page 238, first and second paragraph. The effective delivery results discussed by Eichman et al. include those of Bielinska et al. (*Nucleic Acids Research*, 1996, 24: 2176-2182., cited in the Office Action dated 8/23/05 in the rejection under 35 USC §102, and cited and discussed in the prior Response to Office Action entered 10/31/2007). As discussed in Applicant's prior Response to Office Action, Bielinska et al. teaches that dendrimers of generation 7 to 10 are preferred for use as a transfection agent for delivery and activity of antisense oligonucleotides and plasmid expression vectors coding antisense mRNA. See Bielinska et al., e.g., at page 2178, last paragraph through page 2179 and Figure 4. The teaching of Bielinska et al. amounts to a teaching away of the use of a generation 5 dendrimer as a preferred delivery agent for delivery of nucleic acid conferring activity, since a generation 5 dendrimer did not confer delivery of oligonucleotides having activity. See Bielinska et al., at page 2180, last paragraph and Figure 8.

In sum, when the information known in the art regarding the experiments described in Szoka et al. as well as additional experiments by others are taken together as a whole, it is clear the disclosure of Szoka et al. does not provide an effective disclosure that anticipates the present invention. Further, when taken as a whole, the knowledge in the art comprises a teaching away from the use of a generation 2 to 5 dendrimer for delivery of nucleic acid conferring siRNA activity. Reconsideration and withdrawal of the rejection under 35 USC § 102(b) is thus respectfully requested.

Rejection under 35 USC §102(e) over Frechet et al.

Claims 14, 20, 22-24, and 43 remain rejected under 35 USC §102(e) as anticipated by Frecht [*sic*] et al. (U.S. Patent No. 7,097,856). Applicant respectfully traverses the rejection.

In the first paper setting forth the rejection under §102(e) over Frechet et al., the Office Action mailed 01/03/2007 asserted because Frechet et al. teach use of double stranded RNA, the limitation of nucleic acids capable of mediating RNAi is anticipated because the specification defines siRNA as double stranded RNA molecules. Furthermore, the current Office Action maintains that a dendrimer conjugated to a nucleic acid taught by Frechet et al. reads on a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference.

Frechet et al. teaches making generation 1 to 6 dendrimers that are useful delivery vehicles for a wide variety of agents as covalently conjugated dendrimer-agent compounds. As discussed in the Response filed 05/03/2007, the teaching of Frechet et al. includes using dendrimers as delivery vehicles only in the context of dendrimer *conjugated* (i.e., covalently attached) to a desired agent to be delivered. At column 32, line 45 through column 36, line 43, methods for preparation of conjugated dendrimer-agent linkages are described. For examples of delivery vehicles, at column 22, line 61 through column 32, line

44 Frechet et al. discusses a wide variety of general applications of various therapeutic, diagnostic and analytical agents via conjugation to a dendrimer structure. Thus, Frechet et al. teaches *only* use of therapeutic, diagnostic, and/or analytic agents as a lengthy list of possibilities of agents that may be conjugated directly to dendrimeric structures described (i.e., incorporated with the structure of the dendrimer to generate a single, conjugated compound) for delivery.

The teaching of Frechet et al. provides a very broad disclosure of possibilities of agents that may be used in conjunction with dendrimers described for preparation of conjugate delivery compounds. "A prior art reference that discloses a genus still does not inherently disclose all species within that broad category." See *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1262 (Fed. Cir. 1989); and *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004); and MPEP 2112. Within the very long list of possible agents for delivery, Frechet et al. includes general suggestion of use of nucleic acids in dendrimer-conjugate compounds. Frechet et al. descriptions relating to use of nucleic acids in dendrimer conjugates include a general definition of nucleic acid at column 4, lines 15-33 and a suggestion of possible nucleotide-based drugs at column 29, line 37 through column 31, line 55. The only specific nucleic acids described include aptamers, antisense compounds, and triple helix compounds. In order to anticipate, a reference must disclose each and every element of a claimed invention, either explicitly or inherently. See above discussion and MPEP 2131. No explicit disclosure is provided in Frechet et al. to even suggest use of a nucleic acid capable of mediating RNA interference. At best, the teaching of Frechet et al. is nothing more than an invitation to experiment to find which, if any, particular agents are useful in the suggested dendrimer-agent delivery compounds.

Additionally, as discussed in the above section, in order for a reference to inherently anticipate, a result or characteristic must necessarily be present in the reference. The teaching of Frechet et al. to use nucleic acids having only aptamer, antisense, and triple helix activities evidences that the teaching provides nucleic acid-conjugates include double stranded RNA molecules which include at least some molecules that are not capable of mediating RNA interference. Thus, Frechet et al. does not provide double stranded molecules that are necessarily nucleic acids capable of mediating RNA interference. Therefore, use of molecules mediating RNAi in a dendrimer-conjugate molecule certainly does not necessarily flow from the teaching of Frechet et al., and the disclosure cannot inherently anticipate the present invention.

Furthermore, the disclosure of Frechet et al. does not anticipate Applicant's presently claimed invention because Frechet et al. teaches a delivery compound consisting of a dendrimer conjugated to a desired agent to be delivered (i.e., a single conjugated compound for delivery). In contrast, the present claims recite "a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer

mixed with a nucleic acid capable of mediating RNA interference." As discussed in the prior two Responses to Office Actions, the present invention provides a delivery mixture (i.e., mixture of two separate molecules), which is neither disclosed nor suggested by Frechet et al.

The Office Action maintains a conjugated dendrimer-agent compound according to Frechet et al. meets the limitations of the present claims because the terms mixture or mixing are not defined in the specification; the term mixture does not exclude a dendrimer conjugated to a nucleic acid; and/or the step of a siRNA mixed with a dendrimer does not exclude the step of conjugation. See Office Action at page 10, first and second paragraphs. Applicant respectfully disagrees, and maintains a *compound* consisting of a nucleic acid conjugated to a dendrimer does not read on a *mixture* comprising a delivery agent consisting of a dendrimer mixed with a nucleic acid.

Applicant respectfully submits the interpretation maintained in the Office Action that a conjugated dendrimer-agent compound according to Frechet et al. meets the limitations of the present claims is contrary to the plain meaning of their terms.

> *During examination, the claims must be interpreted as broadly as their terms reasonably allow.* In re American Academy of Science Tech Center, *367 F.3d 1359, 1369, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004)... This means that the words of the claim must be given their plain meaning unless **> the plain meaning is inconsistent with< the specification.* In re Zletz, *893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).* See MPEP 2111.01

Plain meaning refers to the commonly understood meaning of a term by one skilled in the art. See MPEP 2111.01.

Applicant maintains that there is no requirement a term be defined in the specification, since one skilled in the art would readily recognize the claims require a mixture of separate molecules. Furthermore, exactly what was intended by the term "mixture," particularly when the claims are interpreted in view of the specification, would be apparent as consistent with the accepted meaning of "mixture." Applicant further submits "(i)t is appropriate to compare the meaning of terms given in technical dictionaries in order to ascertain the accepted meaning of a term in the art." *In re Barr*, 444 F.2d 588, 170 USPQ 330 (CCPA 1971). For example, a dictionary definition of "mixture" from Webster's New World Dictionary recites:

> *"mixture: ...1 a mixing or being mixed; 2 something made by mixing; esp., a) a combination of ingredients, kinds, etc. b) a yarn or fabric made of two or more different fibers, often of different color;s 3* **Chem.** ***A substance containing two or more ingredients: distinguished from a chemical compound in that the constituents are not in fixed proportions, do not lose their individual characteristics, and can be separated by***

> ***physical means.***" Webster's New World Dictionary, Third College Edition. New York: Simon and Schuster, Inc. 1988. p. 870 (emphasis added).

In view of the specification, one would readily recognize the recitation in the claims requiring "a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference" requires a mixture of at least a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference. Furthermore, since a compound does not include two or more ingredients that can be separated by physical means, which is the accepted meaning of the term mixture, one would also recognize a single compound consisting of a dendrimer conjugated to a nucleic acid is not a mixture. Since Frechet et al. teaches only preparation and use of a conjugated compound consisting of a dendrimer and conjugated agent (e.g., nucleic acid), Frechet et al. does not anticipate the present claims. See, e.g., claims 1, 17, 22, 28, and 32 of Frechet et al.

The Office Action asserts description in the specification wherein a 3' end of an siRNA *can be* conjugated modified with a dendrimer supports that Frechet et al. anticipates the instant claims, citing page 9 of the instant specification. However, Applicant points out whether an siRNA *can be* modified to include a conjugated dendrimer still does not evidence anticipation of the present claims, because a mixture with another separate compound (i.e., a dendrimer) is not necessarily included. The description at page 9 of the specification describes siRNA molecules, and derivatives thereof, which may be used in claimed delivery mixtures. See application as filed at page 9. In view of the context of the application as filed, including the disclosure at page 9 and the disclosure at page 12, one would recognize a modified siRNA conjugated to a dendrimer as described at page 9 would require mixture with a dendrimer compound to meet the description at page 12 and the present claims.

In sum, the disclosure of Frechet et al. does not provide explicit description of a nucleic acid capable of mediating RNA interference; nor is an inherent disclosure of nucleic acid capable of mediating RNA interference provided. Furthermore, the conjugate compounds described and provided by Frechet et al. do not read on "a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference." Thus, Frechet et al. does not provide an effective reference for anticipation of the present invention. Reconsideration and withdrawal of the rejection under 35 USC §102 is thus respectfully requested.

REJECTIONS UNDER 35 USC §103

Applicant appreciates the Examiner's withdrawal of the rejection of claims 14, 19-20, 23-34, 38-42 and 44 under 35 USC §103(a) as being unpatentable over Woolf, Olejnik et al., Grigoriev et al., and Yoo et al.

Applicant appreciates the Examiner's withdrawal of the rejection of claims 14, 17-24 and 32-44 under 35 USC §103(a) as being unpatentable over Yoo et al. in view of Hammond et al., Tuschl et al., and McManus et al.

Applicant appreciates the Examiner's withdrawal of the rejection of claims 14, 17-24 and 32-34, and 38-42 under 35 USC §103(a) as being unpatentable over Yoo et al. in view of Hammond et al., Tuschl et al., and McManus et al.

Rejection under 35 USC § 103(a) over Sato et al, Tuschl et al., and McManus et al., in view of Olejnik et al., and Grigoriev et al.

Claims 14, 19-28, and 33- 44 were rejected under 35 USC § 103(a) over Sato et al. (Clinical Cancer Research 2001), Tuschl et al., and McManus et al., in view of Olejnik et al., and Grigoriev et al., and evidenced by Milhem et al. (International Journal of Pharmaceutics, 2000, Vol. 197: 239-241). The Office Action summarizes Sato et al. as teaching an antisense oligonucleotide mixed with a G4 dendrimer confers efficient internalization of antisense into cells. See Office Action at page 5, second full paragraph. The conclusion of the Office Action is that it would have been obvious to one skilled in the art to use the delivery mixture comprising a dendrimer for an siRNA instead of an antisense molecule, as well as to incorporate modifications such as photocleavable biotin and crosslink using psoralens into the siRNA in view of the disclosures of Tuschl et al., McManus et al., Olejnik et al., and Grigoriev et al. See Office Action at page 7. Further, the conclusion of the Office Action is that one would have a reasonable expectation of success at making a delivery mixture comprising a dendrimer and siRNA, as well as incorporating modifications, "given one would expect the siRNA nucleic acid molecule to be delivery [*sic*] similarly." See Office Action at page 8. Applicant respectfully traverses the rejection.

Applicant respectfully disagrees that the teaching of Sato et al. provides a teaching sufficient such that use of a generation 4 dendrimer as a delivery agent mixed with a nucleic acid capable of mediating RNA interference would be obvious. This assertion of obviousness relies on a finding that one of ordinary skill in the art would have selected a generation 4 dendrimer as a preferred delivery agent from the teaching of Sato et al. for modification of a delivery mixture for delivery of alternative nucleic acids. Based on Sato et al. and the art as a whole, however, Applicant submits a person skilled in the art would not have selected a generation 4 dendrimer as a preferred delivery agent.

First, Sato et al. does not provide evidence of effective delivery of oligonucleotides to cells to confer antisense activity. While the disclosure of Sato et al. provides results of biodistribution studies of injected ^{111}In-oligo-carrier complexes or in vitro cell internalization studies of ^{111}In-oligo-carrier complexes, no evidence that oligonucleotides having antisense activity are effectively delivered to cells is provided. This is acknowledged at page 3611, third full paragraph: "(n)either the scintigrams nor the

biodistribution data provide explicit evidence of internalization of ^{111}In-oligo into the i.p. tumor cells; however, this condition is strongly suggested from the results of the in vitro internalization study." Additionally, at page 3611, last statement of fourth full paragraph Sato et al. acknowledges: "(h)owever, the fate of DNA complexed with dendrimer and/or Av after internalization is still unclear."

Furthermore, a review article published around the time of filing of the present application discussing *in vivo* targeting of antisense further supports a lack of predictability for *in vivo* delivery and targeting of antisense. Hnatowich and Nakamura review the state of the art of antisense targeting. See D.J. Hnatowich and K. Nakamura. *Annals of Nuclear Medicine*, 2004, Vol. 18: 363-368. The publication confirms that, as of 2004, successful *in vivo* antisense targeting had not yet been convincingly demonstrated. See Hnatowich and Nakamura at page 364, second full paragraph; at page 366-367, paragraph transitioning page 366-367; and at page 368, first paragraph. For example, the article states: "(t)o our knowledge, a positive image in a tumored animal by intravenous administration that may be reasonably attributed to antisense targeting has not yet been reported." See Hnatowich and Nakamura at page 367, first paragraph. Furthermore, the review article acknowledges the publication of Sato et al., however, characterizes results of Sato el al. and other studies:

> *...several in vitro and/or in vivo studies have been reported in which control cells have been used. While useful in other ways, the results of these investigations shed little light on whether accumulations were by an antisense mechanism since control oligomers were not used.*

See Hnatowich and Nakamura at page 367, first partial paragraph. When considered as a whole, one skilled in the art would therefore recognize that, at the time of filing of the present application, whether a delivery mixture comprising a dendrimer (even a generation 4 dendrimer) and a nucleic acid could provide effective in vivo delivery to confer antisense activity to cells was at the very best unpredictable and was certainly not obvious.

Second, Sato et al. acknowledges and discusses the many different determining factors affecting delivery of DNA-dendrimer complexes, and furthermore state "...investigators have compared transfection and transcription efficiencies between different dendrimer generations; however the appropriate size to be used as a carrier has not been confirmed yet." See Sato et al., at page 3611, second full paragraph. Maintenance of an obviousness rejection requires no more than routine testing would be expected to generate an effective delivery mixture of nucleic acids. Based on the teaching of Sato et al., however, a person skilled in the art would require more than routine optimization to arrive at a delivery mixture as presently claimed.

Third, publications referenced and relied on by Sato throughout the discussion of investigations demonstrating transfection efficiencies of various dendrimers include those of Yoo et al. and Bielinska et

al. (both cited and discussed in prior Office Actions and Responses), as well as Haensler and Szoka and Tang et al. (cited and discussed above) and others. See Introduction at pages 3606-3607, first two paragraphs, and discussion at page 3611, second through fourth full paragraphs. The teachings of Yoo et al. and Bielinska et al. have been discussed in prior Office Actions and Responses. When taken together as a whole, Yoo et al. and Bielinska et al., as well as the knowledge in the art at the time of the invention support non-obviousness of the claimed invention. See Response to Office Action entered 10/31/2007 at pages 7-17. For all of the same reasons, the present invention Applicant submits the invention as provided would not be obvious to one skilled in the art.

Additionally, Haensler and Szoka and Tang et al. have been discussed in the above rebuttal to the rejection under 35 USC §102(b). For the reasons discussed above, the teachings of Haensler and Szoka and Tang et al. in conjunction with the knowledge in the art at the time of filing of the present invention amount to a teaching away from use of generation 2 to 5 dendrimer for delivery of nucleic acid conferring siRNA activity, and therefore do not support a finding of obviousness of the present invention.

When viewed as a whole, the results and teaching of Sato et al. and the investigations cited therein amount to a teaching that delivery of nucleic acid-dendrimer complexes was unpredictable at best for delivery of antisense activity to cells. Further, given that Sato et al. teaches that delivery of antisense is unpredictable, one skilled in the art would certainly not have a reasonable expectation of success at making a delivery mixture comprising a dendrimer and siRNA, even if one would expect an siRNA nucleic acid molecule to be delivered similarly.

As acknowledged in Applicant's prior responses, Tuschl et al. and McManus teach siRNA molecules and shRNA and microRNA molecules, respectively, which are capable of mediating RNA interference; Olejnik discloses the design, synthesis, and evaluation of a non-nucleosidic photocleavable biotin phosphoramidite (PCB-phosphoramidite) for simple purification and phosphorylation of oligonucleotides; and Grigoriev discloses use of psoralen-oligonucleotide conjugates useful for triple helix formation and cross-linking to DNA following UV irradiation. None of Tuschl et al., McManus, Olejnik et al. or Grigoriev et al., whether alone or in any combination with Sato et al., provide any teaching to lead one skilled in the art to produce a delivery mixture comprising a delivery agent consisting of a generation 2 to 5 dendrimer mixed with a nucleic acid capable of mediating RNA interference. Nor would one skilled in the art expect that such a composition would successfully deliver a nucleic acid capable of mediating RNA interference. Thus, none of Tuschl et al., McManus, Olejnik et al. or Grigoriev et al. remedy the deficiencies of Sato et al., whether alone or in any combination with Sato et al.

In view of the above, Applicant submits that the invention as provided and presently claimed would not be obvious to one skilled in the art; as such the rejection under 35 USC 103(a) should be withdrawn. Reconsideration and withdrawal of the rejection is respectfully requested.

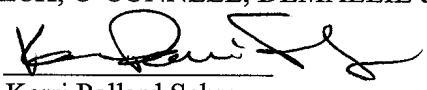
Entry and consideration of the amendments and remarks contained herein is respectfully requested. If at any time a telephone discussion would assist the Examiner and/or expedite prosecution, the Examiner is invited to contact the undersigned.

This paper is being filed timely as it is being filed within the shortened statutory period for response. It is believed that no fees and/or extensions of time are required. In the event that any additional extensions of time, fees and/or credits are necessary, the undersigned hereby authorizes the requisite fees to be charged and/or credited accordingly to Deposit Account No. 50-1582.

Respectfully submitted,

May 23, 2008

MIRICK, O'CONNELL, DEMALLIE & LOUGEE, LLP

By 

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